THE DIAGNOSIS AND TREATMENT OF UNDULANT OR MEDITERRANEAN FEVER.

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(With 2 Charts and Plate VIII.)

The great reduction of the number of cases of Mediterranean or Undulant fever in the Naval and Military forces has been frequently noted since the year 1906, when the prophylactic measures recommended by the Commission of the Royal Society were put into force. Very few cases have been notified since, and in all, the means of infection has generally been easily explained.

From the gradual reduction of the infected goats in Malta itself, the incidence among the civil population too has fallen enormously. In spite of this satisfactory state of things in the chief endemic area, it is a very remarkable fact how greatly the disease has extended into European countries.

In Spain cases have been described by Duran (1906), Ramon y Cajal (1906), Gallart and Férran (1907), and de Cottes (1908). In Portugal it has been noted by Bettencourt (1910). In France cases have been reported from the environs of Paris by Danlos (1908), in the Seine et Marne by Lapeyre (1908), in the Cévennes by Cantaloube (1910), from Marseilles by Simond (1909), Aubert (1910), and Boinet (1911). From Lyons, Rodet, Lesieur and Perret describe cases, and Vedel (1911) does so from Montpellier. Aubert, Cantaloube and Thibault (1910) describe an epidemic in the département du Gare, and Darbois (1911) quotes eleven cases from one house in this district. He shows that the disease was imported by an infected goat of unknown origin, which spread the infection to other goats, the human epidemic following being distinctly due to the diseased animals.

I have also seen undoubted cases from the Riviera. The extension of the epidemic areas far from the sea-board is important, the disease appearing as a strange fever of unknown cause, frequently mistaken for

typhoid, paratyphoid, rheumatism, or rheumatoid arthritis. Under these conditions, methods of diagnosis by means of agglutination reactions have been employed. These when carefully carried out have generally given reliable results, but there are a number of observations recorded which have been most unsatisfactory, positive reactions being obtained with negative cases and *vice versâ*, also different readings of the same serum, so that many clinicians put but little trust in this laboratory test. One of the causes of error is the paradoxical reactions which may be obtained, for when a large series of dilutions are made, good agglutinations may occur at high, yet none at low dilutions of the same serum.

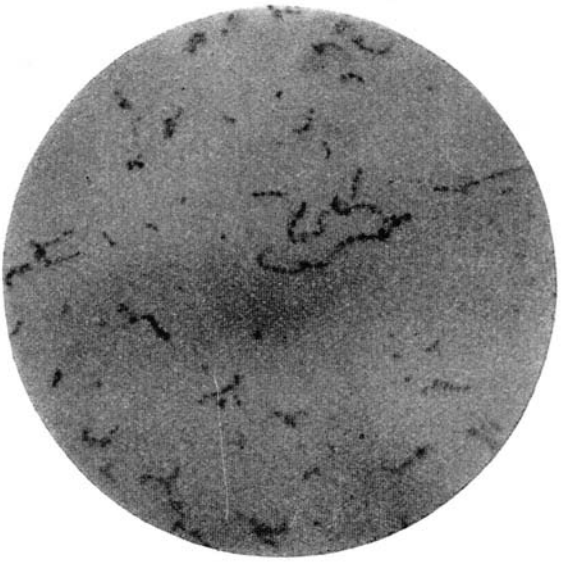
I have here brought forward a number of observations made by different experts, who have been interested in the subject, to show how variable are the results.

Euzière and Roger (1911), while using one strain, found seven cases with clinical signs of Mediterranean fever which gave positive results, and obtained 88 negative results in cases in which the symptoms differed from those of this fever. With two fresh cultures isolated from the blood of two cases of fever, they used the same technique as before, and in 21 cases 7 were positive, of these the greater number were not suspected of having Mediterranean fever. The authors conclude that it is necessary to choose very carefully the culture which is to be used for the diagnostic test. Rouslacroix (1911), replying to this article, says that he has had constant and satisfactory results at dilutions of $\frac{1}{50}$ by the sedimentation method, using two strains of *Micrococcus melitensis*, but that paradoxical reactions were present.

J. Anglada (1912) used four strains. With 110 cases using a dilution of $\frac{1}{80}$, he obtained 66 positive reactions, four only of the cases being Mediterranean fever; with a dilution of $\frac{1}{200}$, five reacted (1 dysentery, and 4 Mediterranean fever), with a $\frac{1}{300}$ dilution only the serum from cases of Mediterranean fever gave reactions.

He also tested these results with serum heated to 56° C. as recommended by Nègre and Raynaud. Out of the 64 sera thus treated, five gave positive reactions (1 Mediterranean fever, 1 dysentery, 1 pneumonia, and 2 syphilis). The heating destroyed the specific agglutinins in the serum of a case of Mediterranean fever. He concludes that it is difficult to base the diagnosis of simple or associated Mediterranean fever on a serum reaction with a $\frac{1}{80}$ dilution.

Nègre and Raynaud (1912) made use of five strains. They found that three of them agglutinated only with specific sera, while two



Micrococcus melitensis. Streptococcic form. × 1500.

https://doi.org/10.1017/S0022172400005143 Published online by Cambridge University Press

agglutinated with non-specific as well as with specific sera. L. Manceaux had analogous results.

The following facts however stand out clearly:

1. Before attempting a serum diagnosis test the culture to be used should be proved to be active with known specific blood, and should not agglutinate with other serum; for, as has been shown, with a series of strains of *M. melitensis* some will give positive reactions with low dilutions of sera in non-Mediterranean fever cases.

2. It is wise as recommended by Nègre to test with both heated and unheated serum.

3. The test should always be carried to high dilutions, $\frac{1}{400}$ or more.

I have therefore made a number of laboratory tests with my own cultures to see how far they bear out the contentions above quoted. The cultures used in all cases were five in number.

A.	Obtained	from	Wright at Netley, 1901.
B.	„	„	Zammit at Malta, 1908.
C.	„	at	Haslar from blood, 1906.
D.	„	at	Haslar from urine, 1906.
E.	„	from	a case with endocarditis, London.

All these gave typical cultural reactions, and agglutinated with Mediterranean fever serum in high dilutions.

I would here like to preface my remarks by a review on the morphology of *M. melitensis*, Bruce. By some authors the organism is classed as a short ovoid bacillus (*B. melitensis* of Hiss) and according to Gordon it is provided with flagella.

There is no doubt that in old laboratory cultures the bacillary forms are very common, these I believe are pure involution characters, for always when these elongated forms are found, abundant minute cocci and diplococci are present. Very frequently the bacillary forms, under a high-power, resolve themselves into cocci and diplococci placed close together. In examining these cultures, small chains are frequently seen, but particularly so in strain (A) when grown on glycerine agar. True streptococci of round or oval elements up to twenty are found, as shown in the micro-photograph (Plate VIII), for which I am indebted to the kindness of Sir W. Leishman. This characteristic, simulating that which occurs with the pneumococcus, is very interesting from a morphological point of view, and probably indicates a racial feature of the organism.

Technique employed. From a 48 hour old agar culture a strong emulsion was made in normal saline solution. Two samples of the sera to be used were obtained; one was heated to 57° C. for half an hour, the other remained unheated. The sedimentation method was employed throughout, and three dilutions were put up ($\frac{1}{40}$, $\frac{1}{100}$, $\frac{1}{400}$), the same amount of emulsion being used for each.

The sedimentation tubes were placed for two hours in the hot incubator and the results recorded. If a positive reaction was to take place clumping would even then be very evident; these tubes were then set aside in the cold, and the results again recorded in 12 hours time. I believe that if the emulsion is strong, and clear serum is used, the macroscopic method is far better than the microscopic for general use; it is easily carried out and the results are definite. Controls with normal blood and known Mediterranean fever blood should always be used, if possible, at the same time.

In this series I have tested the serum from 65 cases, both heated and unheated, with the five strains mentioned above.

With fresh serum from three cases containing the agglutinins of Mediterranean fever, all five strains acted equally well with the unheated serum, but with the heated the results were sometimes variable.

In the first case, higher readings were twice recorded with the unheated than with the heated serum. In the second case the readings were always similar; and in the third, on one occasion a higher reading was obtained with the heated than with the unheated serum.

In these observations, numbering nearly 2000, *once only was a positive agglutination recorded with the control serum*, this was in a case of syphilis with strain (A). In the dilution of $\frac{1}{100}$ of the heated serum in this case the agglutination was strongly marked, whereas in all the other tubes of both heated and unheated sera the results were absolutely negative.

The control bloods employed were mostly taken from syphilitic cases, but a variety of other diseases were also tested, including typhoid, rheumatism, and tuberculosis. With my cultures and the technique employed, the percentage of error is seen to be very small; so that it would appear that in the observations of Anglada (1912), where such great errors were obtained, some factor not present here must have been introduced.

The late L. Nègre and Dr Raynaud have recently demonstrated by absorption experimental work with the agglutinins of the *M. melitensis*, that there exists an organism, indistinguishable otherwise from the

typical *M. melitensis*. This organism they have called the *M. paramelitensis*, the employment of this variety would tend to cause errors in sero-diagnostic work.

This diagnostic method may fail occasionally, owing to the agglutinating bodies being elaborated in such small quantities that they do not give a recognisable reaction. I have had a case in which this occurred, yet the *M. melitensis* was obtained in a pure culture from the spleen. The disease was of eighteen months duration and there was intense cachexia. In similar conditions the absence of agglutination does not negative the diagnosis of Mediterranean fever.

Since this uncertainty with the agglutination test exists, other methods of diagnosis may also be employed with advantage. The culture of the *M. melitensis* from the blood is generally only possible in the early stages of the fever. The isolation of the organism from the urine is very uncertain, for by daily plating the urine of my last two cases no colonies were obtained. In a blood film we often have a rather typical appearance in an advanced case. The red corpuscles (generally about 4,000,000 per c.mm.) show very marked irregularity of shape, colour, and size, particularly in the abundance of microcytes and macrocytes. The white cells show a great reduction of the polymorphonuclears (to about 50%), the lymphocytes and mononuclears are relatively increased, and there may be a few basophiles. This is a condition of secondary anaemia induced by the chronic intoxication produced by the germ, and though confirmatory is not diagnostic.

In the complement fixation test we have another aid, which should always be used if possible. It will almost always give a positive result during the course of the fever, and sometimes for long afterwards. In my series, a positive syphilitic serum used as a control gave a strong positive reaction for Mediterranean fever; on enquiry the fact came out that the man had suffered from a severe attack of the fever *ten* years previously, and had been in my wards at Haslar. He therefore had in his serum two specific immune bodies, each acting with its appropriate antigen. For the purpose of testing the reliability of this method, the serum of a rabbit was used which had been subcutaneously inoculated with 100,000,000 living *M. melitensis* (strain C). The blood of this rabbit agglutinated to $\frac{1}{2000}$ with all five strains. The serum of a case of Mediterranean fever of three months duration, which also showed a high agglutinative value, was tested at the same time. The antigen used was an emulsion in saline solution of a 48 hours growth on agar of *M. melitensis* (strain A), the strength being 100,000,000

per c.mm., the organisms were killed by heat but no antiseptic was added.

The technique used was as follows.

Antigen	Complement 50%	Inactivated serum	Sal. sol.	Haemolytic system	
		Rabbit.			
·1	·1	·1	·7	·5	No haemolysis.
0	·1	·1	·8	,,	Haemolysis.
·1	0	·1	·8	,,	No haemolysis.
·1	·1	0	·8	,,	Haemolysis.
		Patient.			
·1	·1	·1	·7	·5	No haemolysis.
0	·1	·1	·8	,,	Haemolysis.
·1	0	·1	·8	,,	No haemolysis.
		Control.			
·1	·1	·1	·7	·5	Haemolysis.
0	·1	·1	·8	,,	Haemolysis.
·1	0	·1	·8	,,	No haemolysis.

These tests were carried out weekly for two months and 22 controls of different sera were used, with invariably the same result (excepting the case above mentioned).

Treatment.

As regards prophylaxis we must remember that it is not only milk but milk products that are dangerous. I have definite evidence of ice cream and goat cheese being the vehicles of infection. A. Garrow (1911) states that in South Africa he could not always trace the infection to goats' milk, but believed it to be due to the soil infected by goats obtaining access through cracks in the skin.

In treatment there are four main lines to be followed:

(1) Maintain the patient's strength for a prolonged illness by giving as much food as he can assimilate.

(2) Attack the micro-organism by means of vaccines.

(3) Avoid neuritis by administration of yeast or yeast products.

(4) Counteract the secondary anaemia.

Here I only wish to draw attention to (2) and (3).

Vaccines. These to be effective should be freshly prepared, not necessarily autogenous, which is often impossible, but from a good, growing, active laboratory culture.

The vaccine should be given in doses of 100 to 500,000,000, in the loin, at intervals of five to seven days. If this method be used,

when there is only a moderate hectic temperature, it may give excellent results, but is contra-indicated when the pyrexia is continuous or remittent. The accompanying chart (p. 504) of a case lately treated is interesting. In this case the curative action was apparently very marked, for after the second dose the temperature suddenly fell and remained near the normal. Such an abrupt termination of a well-marked case of Mediterranean fever is quite exceptional in my experience. It is of course possible that this favourable result may

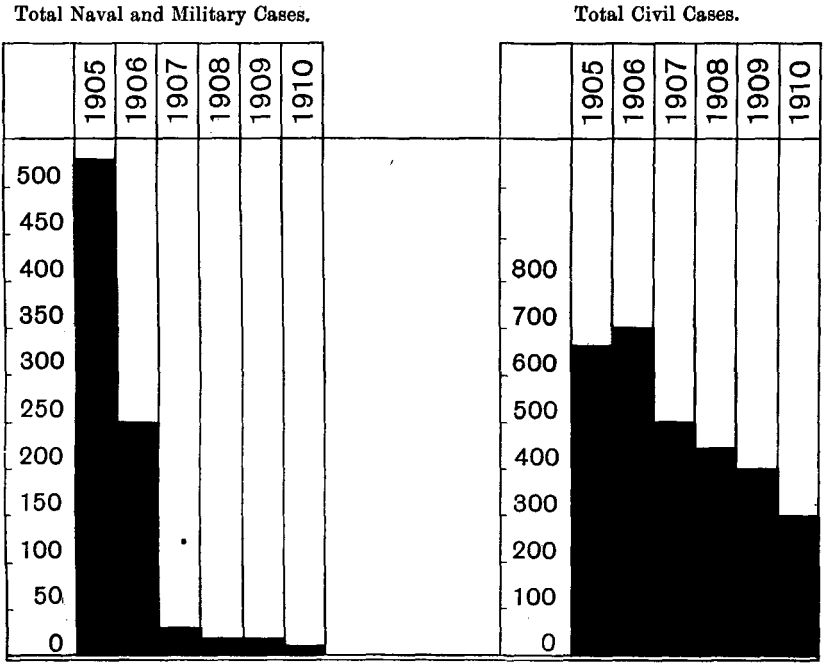


Chart 1. Incidence of Mediterranean fever in the Naval, Military and Civil Population, Malta, 1905–1910. (From Eyre.)

have been a coincidence, but as at the time no other treatment was being used it would appear as a cause and effect. All the other symptoms improved at the same time.

Yeast treatment. One of the most frequent complications of Mediterranean fever is neuritis of a peripheral character. It has long been known that yeast has some beneficial effect in the neuritis of Beri beri, and I have generally employed it in Mediterranean fever in 2 drm. doses, twice a day. It may be that in this fever the neuritis is not

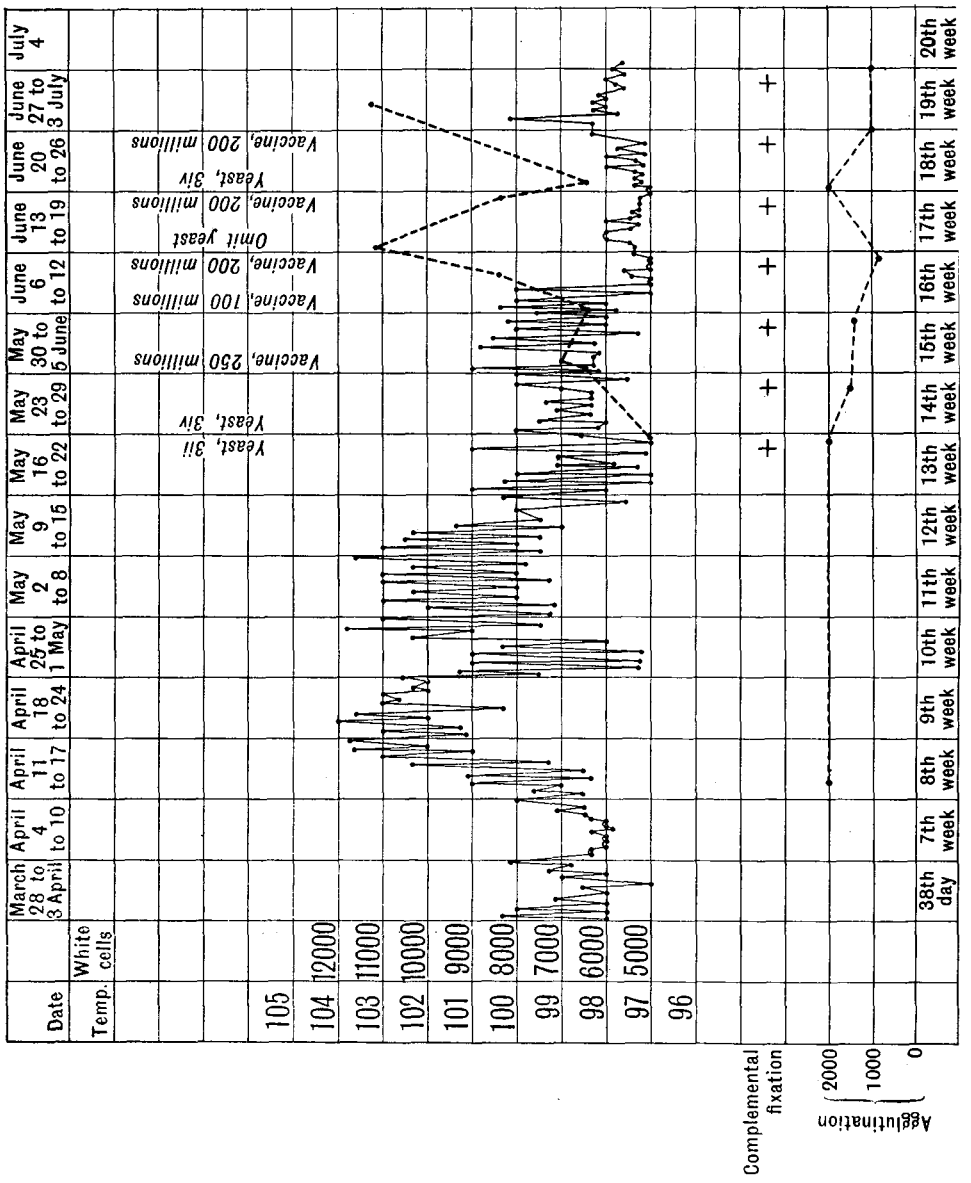


Chart 2. Mediterranean fever treated with vaccine and yeast showing agglutination and leucocyte curves.

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directly due to the toxic action of the *M. melitensis* on the nerve cells, as was believed, but that there is a drain on the nerve tissue to produce the necessary "Vitamine" required in health. C. Funk suggests that this is the cause of the neuritis in Beri beri. Yeast, which apparently contains more than one "Vitamine," may prevent this loss in the nerve tissue; it also appears to have a beneficial effect in increasing the number of polymorphonuclear cells.

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